

HCV Testing Cost-Effective Alternative To Treating Advanced Disease

According to the Centers for Disease Control and Prevention, the number of new hepatitis C infections in the United States (30,000 in 2003) is only about a tenth what it was in 1989 (291,000), the year before the hepatitis C virus (HCV) was discovered. That's progress, but much more can be done to diagnose and treat people with HCV.

More than 4 million Americans are infected with HCV. "Less than 20 percent have been diagnosed, and only about half of those patients have been treated," explains Mitchell L. Shiffman, MD, chief of hepatology and medical director of the liver transplant program at Virginia Commonwealth University Medical Center. "The only way to reduce the burden of hepatitis C

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and potential complications is to identify these individuals and treat them. We can cure about half of them with current therapy."

Even appropriate management of patients who aren't cured would improve population-health status and productivity, reduce the rate of new infections, and cut the number of liver transplants — most of which are performed on HCV patients. The economic case for aggressive diagnosis and treatment of hepatitis C would seem like a slam dunk, compared to the cost of a liver transplant (see table, below).

UNDER THE SURFACE

Unfortunately, applying what we already know about hepatitis C is not a slam dunk. For starters,

the natural history of hepatitis C makes it hard to diagnose. People infected with hepatitis A and B know they're sick because they have fatigue, jaundice, and fever, and they can be screened for elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels to detect impaired liver function.

Those with HCV could be asymptomatic for decades, with underlying liver injury even if liver-function tests are normal. Once HCV has been diagnosed, a full evaluation includes viral load testing, characterization of the HCV genotype, and a biopsy to assess the severity of liver disease. Depending on the results, a patient may be a candidate for drug therapy.

"They're not at risk to develop

Comparing costs of HCV interventions

HCV diagnostic testing ¹	HCV therapy ¹	Liver transplantation ²
ELISA antibody screening test (CPT 86803) \$77–104	Interferon and ribavirin (48-week course) \$24,000	Negotiated case rate (includes organ procurement, hospital, and physician charges) \$268,800
Confirmatory RIBA antibody test (CPT 86804) \$108–138	7 HCV RNA tests \$1,106–1,813	
RNA test (CPT 87522) \$158–259	HCV genotyping test (CPT 87902) \$719	Services not usually part of a negotiated case rate (evaluation, follow-up, outpatient immunosuppressant maintenance therapy) \$124,000
Liver biopsy \$2,747		
Totals \$3,090–3,248	\$25,825–26,532	\$392,800

ELISA=enzyme-linked immunosorbent assay, HCV=hepatitis C virus, RIBA=recombinant immunoblot assay.

¹ Gross charges, before reimbursement, not including provider charges.

² Estimated U.S. average 2005 first-year billed charges per transplant.

SOURCES: BILL DUNBAR AND ASSOCIATES, INDIANAPOLIS; MILLIMAN RESEARCH REPORT: "2005 U.S. ORGAN AND TISSUE TRANSPLANT COST ESTIMATES AND DISCUSSION," BY NICKOLAS J. ORTNER; VIRGINIA COMMONWEALTH UNIVERSITY MEDICAL CENTER

complications until they get cirrhosis, and only 20 percent of patients with chronic hepatitis C develop cirrhosis," says Shiffman. "If a patient has mild hepatitis C, you've got decades to monitor that patient to determine his place in the spectrum before you need to commit to drug therapy."

Diagnosing HCV infection is fairly straightforward, says Frederick Nolte, PhD, director of the Clinical Microbiology and Molecular Diagnostic Laboratories at Emory University Hospital, in Atlanta. First, there's a relatively inexpensive enzyme-linked immunosorbent assay (ELISA) serological antibody screening test. A positive result doesn't necessarily mean active infection, but only that the patient has been exposed to the virus. In fact, about 15 percent of those infected with HCV spontaneously resolve the virus with no medical intervention and have no further evidence of hepatitis C.

Next comes a recombinant immunoblot assay (RIBA), another serological antibody test to confirm the results. Only low positive ELISA tests need to be confirmed with RIBA. A positive serological test is usually followed by a polymerase chain reaction (PCR)-based nucleic acid test, which detects HCV RNA in the serum. The costs of the supplemental RIBA and PCR tests are similar. A positive HCV RNA test is evidence of active HCV infection.

HCV RNA tests not only detect viral RNA but also quantitate its concentration in the blood (i.e., the viral load) and characterize the genotype of the hepatitis C virus. HCV RNA tests are critical in establishing a diagnosis, in deciding whether a liver biopsy is indicated, in dosing therapy, in monitoring and adjusting therapy, and in establishing whether a hepatitis C patient is cured.

GENOTYPES: PREDICTORS OF SUCCESS

"Not everybody with hepatitis C necessarily goes directly to therapy," Nolte points out. "This can be a sort of benign infection, and it could be 10 years before someone requires therapy. But if the physician makes the decision to treat a patient, both the viral load and genotype can predict response to therapy. For example, high viral load and genotype 1 are predictors of poor response."

Of the six HCV genotypes, types 1, 2, and 3 are most prevalent in the United States. Type 1 infections respond differently than types 2 or 3 to the current combination therapy of pegylated interferon, an immune modulator, and ribavirin, an antiviral agent. According to Shiffman, a 12-month course of therapy succeeds in about 45 percent of patients infected with type 1, the most difficult to eradicate. Types 2 and 3 are much more sensitive to therapy and can be eradicated in 70 to 90 percent of patients with 4 to 6 months of therapy.

The goal of hepatitis C therapy is to eradicate the virus so it can no longer be detected by a sensitive HCV RNA test. Sustained virologic response (SVR) is achieved if the HCV becomes undetectable during therapy and remains undetectable six months after the end of therapy. But current treatment algorithms are being challenged as new data become available.

For example, a recent study suggests that "partial response" patients — i.e., those whose viral load drops substantially during treatment but not to the point of being undetectable — benefit from this lower HCV RNA and may achieve SVR if therapy is continued for 72 weeks. Several large studies are now looking into this possibility.

Shiffman cites other recent data

showing that the time it takes for patients to become HCV RNA undetectable may predict their odds of achieving SVR or relapse after therapy ceases, even if the dosage is reduced to mitigate side effects. Genotype 1 patients who are HCV RNA undetectable within one month of starting treatment have a 90 percent chance of SVR, while the chances decline to 20 percent with six months of treatment.

MONITOR VIRAL LOAD

The key, Shiffman emphasizes, is monitoring viral load monthly during the first three months of therapy — or up to six months, depending on the viral response during the first three months. He cautions that ordering an HCV RNA test at the end of six or twelve months of therapy and concluding that therapy has failed because the virus is still detectable may mean missing a patient who is responding and may still achieve SVR.

None of this technology or emerging clinical trial data will come into play unless HCV is diagnosed. Because someone infected with HCV can be asymptomatic for decades, Shiffman admits the likelihood of an early diagnosis is slim unless the patient or physician knows the risk factors for infection and follow up with an antibody test. The most significant risk factors include blood transfusions received in the early 1990s or earlier and intravenous drug abuse.

"Physicians have to ask patients about these risk factors," says Shiffman. Otherwise, he says, "They won't know to test that patient for hepatitis C, hepatitis B, HIV, or other communicable diseases." **BH**

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